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Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnosis by conventional and contrast enhanced US findings

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Abstract:	Objective: To clarify the details of homogenously enhancing lesions on contrast-enhanced ultrasonography (CEUS) and also to elucidate whether their differential diagnosis is possible. Methods: 73 homogenously enhancing lesions on CEUS were retrospectively selected. Two radiologists first assessed conventional US findings alone in consensus to differentiate malignant vs benign lesions. Then, qualitative and quantitative CEUS findings were analyzed to determine the useful findings for differential diagnosis. Determined CEUS findings were applied to the indeterminate lesions based on conventional US findings to see whether CEUS may improve the diagnostic performance. Results: There were 42 cancers (58%) out of 73. Sensitivity and specificity using conventional US findings alone were 91% and 55%, respectively. Among the CEUS findings tested, multivariate analysis revealed only the type 3 enhancement pattern, which indicates larger enhancing area than the precontrast hypoechoic lesion, was related to malignity ($p<0.05$). By adding this information, however, no improvement was achieved in the diagnostic performance as determined by conventional US findings. Conclusions: Approximately half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulous assessment of the conventional US findings, rather than CEUS findings.

Author Comments:	April 13, 2016 Editorials Board Japanese Journal of Radiology Subject: Manuscript, " Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnoses ", Ritsuko Fujimitsu, et al Gentlemen: Enclosed are the re-revised version of the above manuscript, with a complete set of figures, which we hereby submit for possible publication in Japanese Journal of Radiology as an original research. We greatly thank the assistant editor for his or hers invaluable suggestions to our manuscript. We made corrections as suggested by the assistant editor's comments to improve our manuscript. We hope our revision is sufficient for final acceptance in Japanese Journal of Radiology. Thank you for your consideration. Sincerely, Kengo Yoshimitsu, M.D., Ph.D. Department of Radiology Faculty of Medicine, Fukuoka University 7-45-1, Nanakuma, Jonan-ku, Fukuoka, JAPAN, 814-0180 (Fax) 92-801-1011 (Phone)92-864-6652 (e-mail) kengo@fukuoka-u.ac.jp

Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnosis by conventional and contrast enhanced US findings

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Abstract

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Results: There were 42 cancers (58%) out of 73. Sensitivity and specificity using conventional US findings alone were 91% and 55%, respectively. Among the CEUS findings tested, multivariate analysis revealed only the type 3 enhancement pattern, which indicates larger enhancing area than the precontrast hypoechoic lesion, was related to malignity ($p<0.05$). By adding this information, however, no improvement was achieved in the diagnostic performance as determined by conventional US findings.

Conclusions: Approximately half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulous assessment of the conventional US findings, rather than CEUS findings.

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Contrast-enhanced ultrasound; homogeneously enhancing lesion; differential diagnosis

INTRODUCTION

With the advent of contrast agent for ultrasonography, several researchers have applied this technique, namely contrast enhanced ultrasonography (CEUS), to breast imaging, and not a few promising data have been published in terms of malignancy vs benignity differentiation [1-4]. Generally, it has been reported that irregularly or peripherally enhancing lesions are malignant, whereas homogeneously enhancing ones are benign [1-3]. However, we encounter considerable number of "exceptional" cases in daily practice, which are against the above mentioned rules, particularly for the latter [4-6]. To our knowledge, little has been investigated specifically focused on the differential diagnosis of homogeneously enhancing lesions on CEUS.

This study was conducted, therefore, to clarify the clinico-pathological details of "homogeneously enhancing lesion" on CEUS, and to elucidate whether differentiation between malignant and benign lesions in this particular cohort is possible.

MATERIALS AND METHODS

Between October 2012 and August 2015, 134 patients with 161 suspected breast lesions underwent CEUS in our institute. Among these, the lesions which showed homogeneous enhancement at their peaks, and also for whom final pathological diagnoses were obtained, were retrospectively recruited. In our institute, CEUS is routinely performed as a presurgical procedure, or for patients whose diagnosis is indeterminate or questionable based on conventional radiological workup. Our institutional review board waved obtaining informed consent because of its retrospective nature.

CEUS was performed with a clinical ultrasound unit (LOGIQ E9, GE HealthCare, Milwalkee, WI). Conventional and contrast-enhanced US images were obtained with a ML 6-15MHz and a SL 9MHz linear probes, respectively. Mechanical index was set at 0.2-0.21. After confirming that the target lesions were well visualized at the center of field-of-views, bolus injection of contrast medium (Sonazoid, Daiichi Sankyo, Tokyo, Japan) of 0.015 mL/kg was performed from the antecubital vein, followed by 10mL saline flush. The target lesions were then continuously observed for 90s using real-time grayscale harmonic imaging, the whole process of which was video-

recorded.

All sonographic images and videos were reviewed by two experienced radiologists (RF and MS) who were experienced in breast sonographic imaging and blinded to the pathological results. First, the conventional US images alone were evaluated, and the confidence level of diagnosing malignity was determined using 5-poin scale in consensus, with scores 1, 2, 3, 4, and 5 indicating definitely benign, possibly benign, indeterminate, possibly malignant, and definitely malignant, respectively, according to the previously reported criteria, namely, Breast Imaging Reporting and Data System (BI-RADS) 2013 [7] for mass lesions and those defined by Ko et al. [8] for non-mass-like lesions. As for mass lesions, the final score of a certain patient was determined based on the total balance of the assessment for each finding of BI-RADS 2013 (Table 1); more specifically, the all findings listed in Table 1 were checked for each lesion, and if findings favoring malignity or benignity were dominant, scores 4-5 or 1-2 were given, respectively; if these were similar in number, score 3 was given. As for non-mass lesions, types Ib and IIb, were considered malignant, whereas the rest were benign or indeterminate (Table 1). Scores 4 and 5 were regarded as suggesting

malignancy, respectively, and sensitivity and specificity were calculated.

Then, the enhancement patterns of the lesions on CEUS were reviewed and divided into the following three groups; type1, in which the degree of enhancement of the lesions was almost equal to the surrounding breast tissue, type 2, where the degree of enhancement was greater than that of surrounding tissue with the area of enhancement being approximately the same as the precontrast hypoechoic lesion in size, and type 3, in which the degree of enhancement was greater than that of surrounding tissue, and the area of enhancement was larger than the hypoechoic lesion on the precontrast images. On the dynamic phase of contrast enhancement, one radiologist (RF) manually placed region-of-interest to cover the whole lesion as visualized on the initial images before contrast arrival, and time-intensity-curve (TIC) was created, and following indices were semi-automatically calculated: Axk value was defined as the slope of the tangent at the beginning of TIC

; time to peak (TTP) was defined as the time period in sec between the beginning point to the peak of TIC: ascending slope (AS) was defined as the slope between the beginning point to the peak of TIC.

The correlation between these CEUS parameters (enhancement patterns,

Axk, TTP, and AS) and malignity vs benignity were assessed and significant factors for differentiation were sought. Significant factors, if present, were applied to the above mentioned score 3 groups, namely indeterminate lesions when assessed solely with conventional US image findings, and sensitivity and specificity were again calculated to check whether adding CEUS information might improve the diagnostic capability.

For statistical analyses, Wilcoxon Kruskal-Wallis test, Fisher's exact probability test, and $\chi 2$ test, were used for univariate analyses, and logistic regression test was used for multivariate analysis. P values of less than 0.05 were considered significant. The statistical software used was JMP version 11 (SAS corporation, Cary, USA).

RESULTS

There were 73 patients with 73 lesions with age ranging from 34 to 80 years old (mean 53.2), including 10 fibroadenoma/phyllodes tumors, 12 intraductal papillomas, 19 ductal adenocarcinoma in situ (DCIS), 23 invasive ductal adenocarcinomas (IDC), and 9 other non-specific benign lesions (NSBL). Namely, 58% (42/73) of homogeneously enhancing lesions were malignant in our patient population. All NSBL showed fibrocystic change or adenosis with or without slight inflammatory cell infiltration. The lesions size ranged from 4 to 85 mm in their maximum dimension, with malignant lesions (19.5± 15.1mm) being larger than benign ones (10.5 ± 6.3mm). Among these, histological diagnoses were made by surgical resection, percutaneous needle biopsy, and cytology for 50, 19, and 4 lesions, respectively.

Diagnosis solely based on conventional US findings

As for mass lesions, two, one, 12, 27, and 7 lesions were given score 1, 2, 3, 4, and 5, respectively; as for non-mass lesions, there were 0, 0, 6, 10, and 8. In total, two, one, 18, 37, and 15 lesions were graded as score 1, 2, 3, 4, and 5, respectively by the two reviewers. The three lesions given scores 1 or 2 were

all benign, and 15 lesions given scores 5 were all malignant. Those scored as 3 (indeterminate lesions) included 14 benign and 4 malignant lesions. Those scored as 4 (probably malignant) included 14 benign and 23 malignant lesions. Thus, when scores 4 and 5 were considered to suggest malignity, sensitivity, specificity, and accuracy were 90.5% (38/42), 54.8% (17/31), and 75.3% (55/73), respectively.

CEUS findings

The details of the CEUS findings vs histological classification are shown in Table 2. When histology was simply divided into benign vs malignant, enhancement pattern was the only significant factor, suggesting type 3 enhancement pattern was significantly related to malignancy. When each disease entity was separately considered, univariate analysis suggested enhancement pattern and Axk were significant factors, with type 3 enhancement pattern being associated with IDC, and Axk of NSBL being smaller than those of IP (Table 1). No other indices were significantly different among the disease entities. Multivariate analysis revealed that only enhancement pattern was independently significant with the likelihood ratio

χ^2 (Chi-square) values of 13.1.

Diagnosis using both conventional US and CEUS findings

The significant parameter in CEUS finding, namely enhancement pattern, was attempted to be incorporated into the diagnosis using conventional US findings, however, all 8 lesions showing type 3 enhancement pattern had already been diagnosed as malignant by conventional US findings (two and six lesions were scored as 5 and 4, respectively). Thus, incorporating CEUS finding into conventional US findings did not improve diagnostic performance in terms of malignant vs benign differentiation.

Representative cases are shown in Fig.s 1-3.

DISCUSSION

Our results suggested homogeneously enhancing lesions are not necessarily benign, but considerable number of malignancy (approximately 60% in our cohort) can be included in this group of lesions. Among these, approximately 75% of lesions can be correctly diagnosed as benign or malignant by conventional US findings alone, but one quarter of them (18/73) remain indeterminate.

As for CEUS findings, our factor analysis revealed enhancement pattern and Axk values were significantly related to the final diagnoses of the lesions.

Actually, all 8 lesions showing type 3 enhancement pattern (the degree of enhancement was greater than that of surrounding tissue, and the area of enhancement was larger than the hypoechoic lesion on the precontrast images) were IDC. Histopathological correlation revealed two of these lesions showed strong lymphocytic infiltration around the marginal areas of the lesions (Fig.3). Similar observation, namely peritumoral enhancement around IDC, has already been reported, which have been attributed to DCIS component around IDC, adenosis with lobular hyperplasia or inflammatory cell infiltration around IDC [5, 9-10]. A “crab-craw like microvascular

architecture" or increased microvessel density or vascular endothelial growth factor expression may be related to this findings [5, 10-12].

In contrast to the previous report [1, 6, 9], quantitative indices derived from TIC did not serve to the differential diagnosis, except for Axk values, which were useful only in differentiating NSBL from IP. NSBL and IP tended to show lower and higher Axk values, respectively, among the disease entities included in this study. NSBL in our population consisted of fibrocystic change or adenosis with or without slight inflammatory cell infiltration, possibly representing mastopathy or chronic mastitis. We presume angiogenic features may be similar regardless of it benignity or malignity in this particular cohort. In addition, multivariate analysis revealed that only enhancement pattern, not Axk, was the independently significant factor in the differential diagnosis.

Adding the significant factor derived from CEUS, namely enhancement pattern, however, did not improve diagnostic performance solely based on conventional US findings. All lesions showing type 3 enhancement pattern had readily been diagnosed as malignant, using conventional US findings (Table 1). Thus, CEUS findings, either qualitative or quantitative, added little

to the differential diagnosis of homogeneously enhancing lesions on CEUS. We therefore recommend looking back the conventional US findings meticulously when dealing with the lesions in this particular cohort.

There are several limitations in this study, in addition to the retrospective nature. First, although the total number of subjects were over 70, both benign and malignant lesions included various entities of limited number, and therefore our result may not be applicable to different cohort of different disease configuration. Ideally, our results should have been tested in another cohort consisting of homogeneously enhancing lesions. Second, because the enhancement pattern of the lesions was assessed as compared to that of the background breast tissue, the results would be affected by the condition of the background tissue, for example menstrual cycle or age-related fatty change, in addition to that of the lesions themselves. Third, placement of ROI to create TIC and subsequent quantitative indices measurement was performed by one radiologist, which may have caused some bias in the results. Fourth, qualitative assessment was made by two radiologists in consensus, not by independent interpretation, which also may have resulted in some bias. Further prospective study with larger population and meticulous design

would be needed to solve these problems.

In conclusion, radiologists should be aware that almost half of homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulously referring to the conventional US findings, not to CEUS findings.

References

1. Zhao H, Xu R, Ouyang Q,ChenL, Dong B, Huihua Y, Contrast-enhanced ultrasound is helpful in the differentiation of malignant and benign breast lesions. Euro J Radio. 2010; 73: 288-293

2. Du J, Wang L, Wan CF, Hua J, Fang H, Chen J, Li FH. Differentiating benign from malignant solid breast lesions: Combined utility of conventional ultrasound and contrast enhanced ultrasound in comparison with magnetic resonance imaging. Eur J Radiol 2012; 33: 3890–3899.

3. Miyamoto Y, Ito T, Takada E, Omoto K, Hirai T, Moriyasu F. Efficacy of Sonazoid (Perflubutane) for contrast-enhanced ultrasound in the differentiation of focal breast lesions: Phase 3 multicenter clinical trial. AJR 2014; 202: W400-407

4. H.Liu, YX Jiang, JB Liu, et al. Evaluation of breast lesions with contrast-enhanced ultrasound using the microvascular imaging technique: Initial observations. The Breast 2008; 17: 532-539

5. H.Liu, YX.Jiang, JB Liu, et al. Contrast-enhanced breast ultrasonography Imaging features with histopathologic correlation. J Ultrasound Med. 2009; 28: 911-920

6. Wan CF, Du J, Fang H, et al. Evaluation of breast lesions by contrast enhanced ultrasound: Qualitative and quantitative analysis. Euro J Radio 2012:81:e444-e450

7. American College of Radiology. BI-RADS® – Ultrasound 2013. http://www.acr.org/Quality-Safety/Resources/BIRADS/Ultrasound

8. Ko KH, Hsu HH, Yu JC, et al. Non-mass-like breast lesions at ultrasonography: feature analysis and BI-RADS assessment. EJR 2015;84:77-85

9. Jiang YX, Liu H, Liu JB, et al. Breast tumor size assessment: Comparison of conventional ultrasound and contrast-enhanced ultrasound. Ultrasound in Med. & Biol. 2007; 33: 1873-1881.

10. Du J, Li FH, Fang H, et al. Microvascular Architecture of Breast Lesions; Evaluation With Contrast-Enhanced Ultrasonographic Micro Flow Imaging. J Ultrasound Med. 2008; 27: 833-842

11. YJ.Li, G Men, Y Wang, et al. Perfusion heterogeneity in breast tumors for assessment of angiogenesis. J Ultrasound Med. 2013; 32:1145-1155

12. Liu H, Jiang YX, Dai Q, et al. Peripheral enhancement of breast cancers on contrast-enhanced ultrasound: Correlation with microvessel density and vascular endothelial growth factor expression. Ultrasound in Med. & Biol., 2014;40: 293–299

Table 1 Criteria for malignity and benignity of the lesions based on conventional sonographic findings before contrast enhancement

		benign	indeterminate	malignant
Mass lesion [7]*				
	shape	Oval	Round	Irregular
	orientation	Parallel to the skin		Not parallel to the skin
	margin	Circumscribed	Microlobulated	angular, indistinct, spiculated
	internal echo	Aechoic, hyperechoic	Isoechoic, hypoechoic	Complex,
	posterior acoustic features		Enhancement, None	shadowing, combined
	calcification			In mass, intraductal
	architectural distortion			yes
	Duct change			yes
Non-mass lesion [8]**				
	types		type Ia, type IIa, type III, type IV	type Ib, type IIb

* Original reference #7 includes other factors including skin appearances, Doppler or elastography information. However, in our patients, none showed skin thickening, skin retraction, or edema: Doppler sonography and elastography were obtained in limited number of cases. These findings were therefore omitted in the table.
** Type I ductal non-mass-like (NML) pattern: parallel orientation of multiple duct-like structures without calcifications

(type Ia) or with associated calcifications (type Ib). Type II nonductal NML pattern: a geographic or mottled area that does not give a discrete mass, and may present without calcifications (type IIa) or with associated calcifications (type IIb). Type III NML pattern: associated with architectural distortion, Type IV NML pattern: associated with posterior acoustic shadowing [8].

Table 2 Correlation between contrast-enhanced US findings and histology

CEUS findings	benign	malignant	P values	Disease entities					P values	
				benign			malignant			
				FA/Phyl	IP	NSBL	IDC	DCIS	Uni	Mul
Ehn.pattern Type 1/2/3	14/17/0	23/11/8	0.004	3/7/0	4/8/0	7/2/0	11/4/8	12/7/0	0.01	0.0005
Axk	6.5 ± 3.2	7.1 ± 3.5	NS	6.8 ± 2.5	8.2 ± 3.3	4.1 ± 2.0	7.4 ± 4.2	6.8 ± 2.6	0.044*	NS
TTP	9.6 ± 3.0	9.7 ± 4.8	NS	9.3 ± 2.2	8.9 ± 1.4	10.1 ± 5.8	10.8 ± 4.6	8.9 ± 4.5	NS	
AS	2.2 ± 0.8	2.2 ± 1.0	NS	2.3 ± 0.7	2.4 ± 0.5	1.9 ± 1.1	2.2 ± 1.1	2.2 ± 0.9	NS	

CEUS: contrast-enhanced ultrasonography, Enh.pattern: enhancement pattern, Axk: the slope of the tangent at the beginning of time-intensity-curve, TTP: time to peak, AS; ascending slope.

FA: fibroadenoma, Phyl: phyllodes tumor, IP: intraductal papilloma, NSBL: non-specific benign lesion, IDC: invasice ductal carcinoma, DCIS: ductal carcinoma in situ, Uni: univariate analysis, Mul: multivaraiate analysis

※ indicates NSBL vs IP

Figure legends

Fig.1 Pathologically proven fibroadenoma in a 65 year-old woman.

1a Conventional sonography revealed an oval shaped, well circumscribed mass of 10 mm in its greatest dimension, with an internal echogenicity similar to that of the adjacent adipose tissue, associated with slight posterior acoustic enhancement (arrows).

1b Contrast-enhanced sonography showed homogeneous enhancement of the lesion, corresponding to type 2 enhancement pattern (arrows). Axk value was semi-automatically calculated to be 3.82 (time-intensity curve not shown).

1c Microscopic appearance of the lesion (hematoxylin and eosin staining, original magnification x100). Arrow indicate the boundary of the lesion.

Fig.2 Ductal carcinoma in situ in a 41 year-old woman.

2a Conventional sonography reveals a well-demarkated hypoechoic lesion without mass formation, measuring 30 mm in its greatest dimension (arrows).

2b Contrast-enhanced sonography showed homogeneous enhancement of the whole lesion, which is indistinguishable from the background tissue, in keeping with type 1 enhancement pattern. Axk value was semi-

automatically calculated to be 8.22 (time-intensity curve not shown).

2c Microscopic appearance of the lesion (hematoxylin and eosin staining, original magnification x200). Arrow indicate the calcification within the lesion..

Fig.3 Invasive ductal carcinoma in a 49 year-old woman.

3a Conventional sonography reveals an irregularly shaped hypoechoic mass of 24 mm in its greatest dimension, showing spicualted margin and slight posterior shadowing (arrows).

3b Contrast-enhanced sonography showed homogeneous enhancement, the size of which was larger than the hypoechoic area as observed on precontrast image, in keeping with type 3 enhancement pattern. Axk value was 3.08 (time-intensity curve not shown)

3c Pathological specimen reveals prominent lymphocytic infiltration (arrows) around the margin of the lesion (C), which may explain the extensive peritumoral enhancement (hematoxylin and eosin stain, original magnification x 200).

Figure

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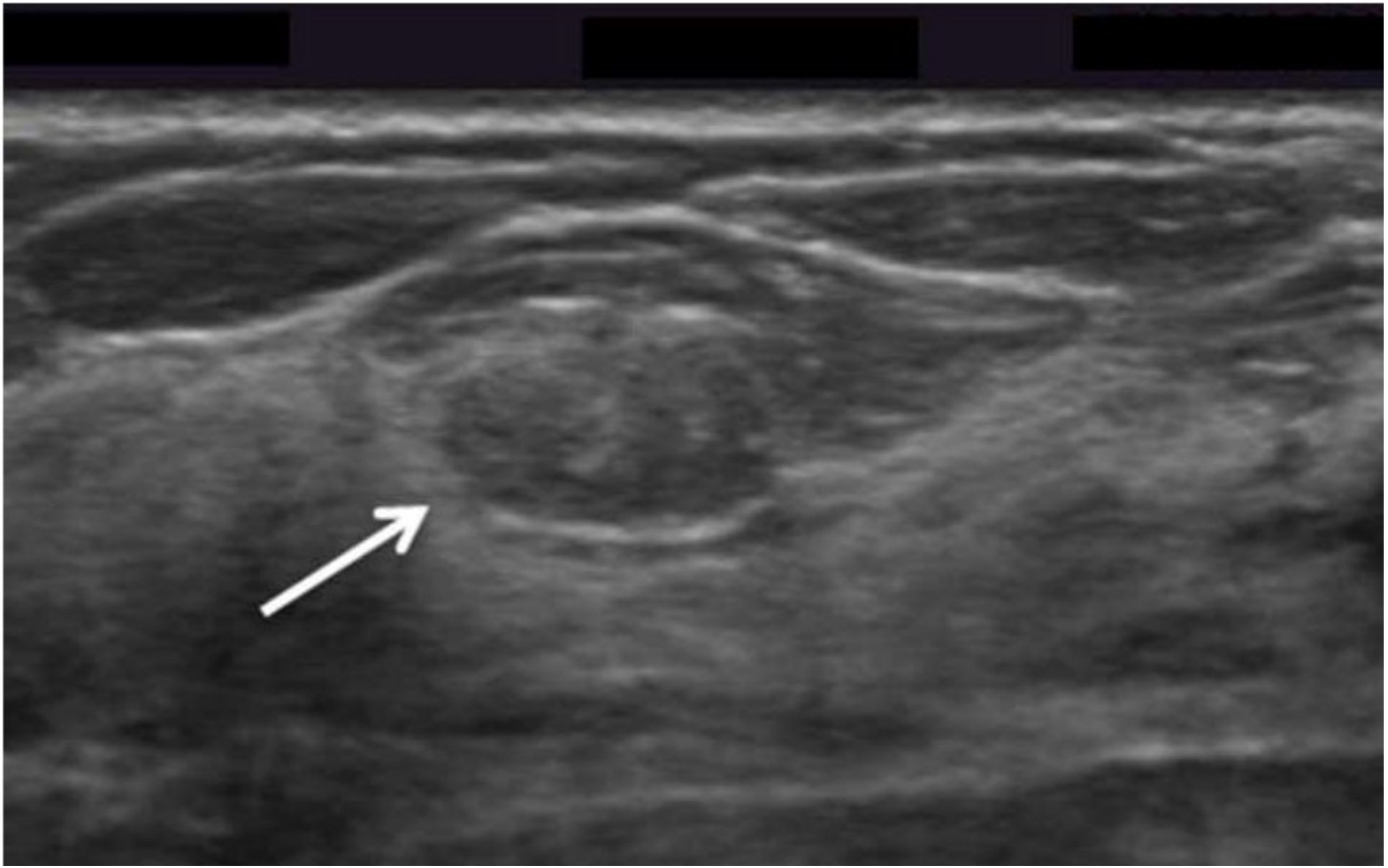

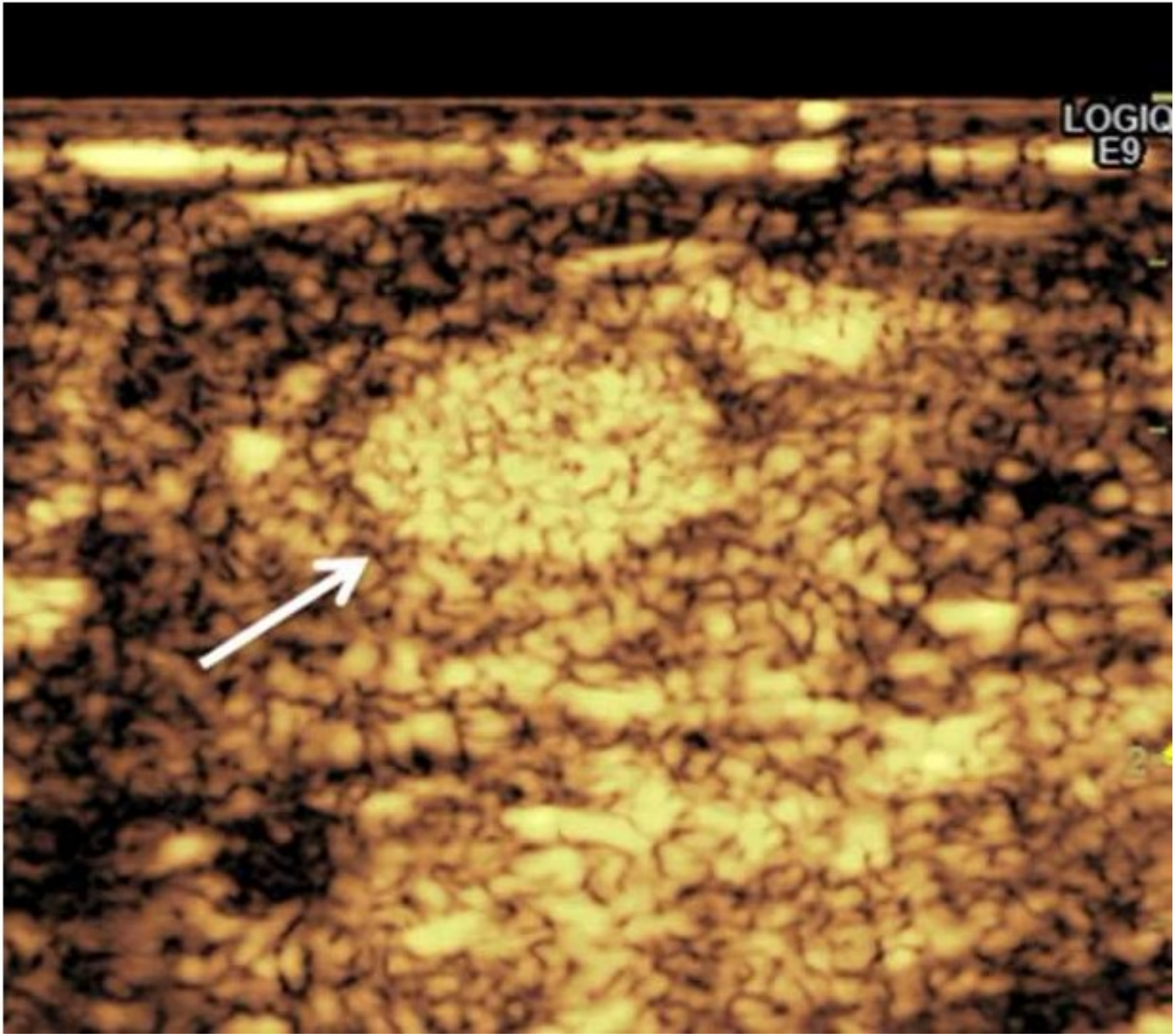
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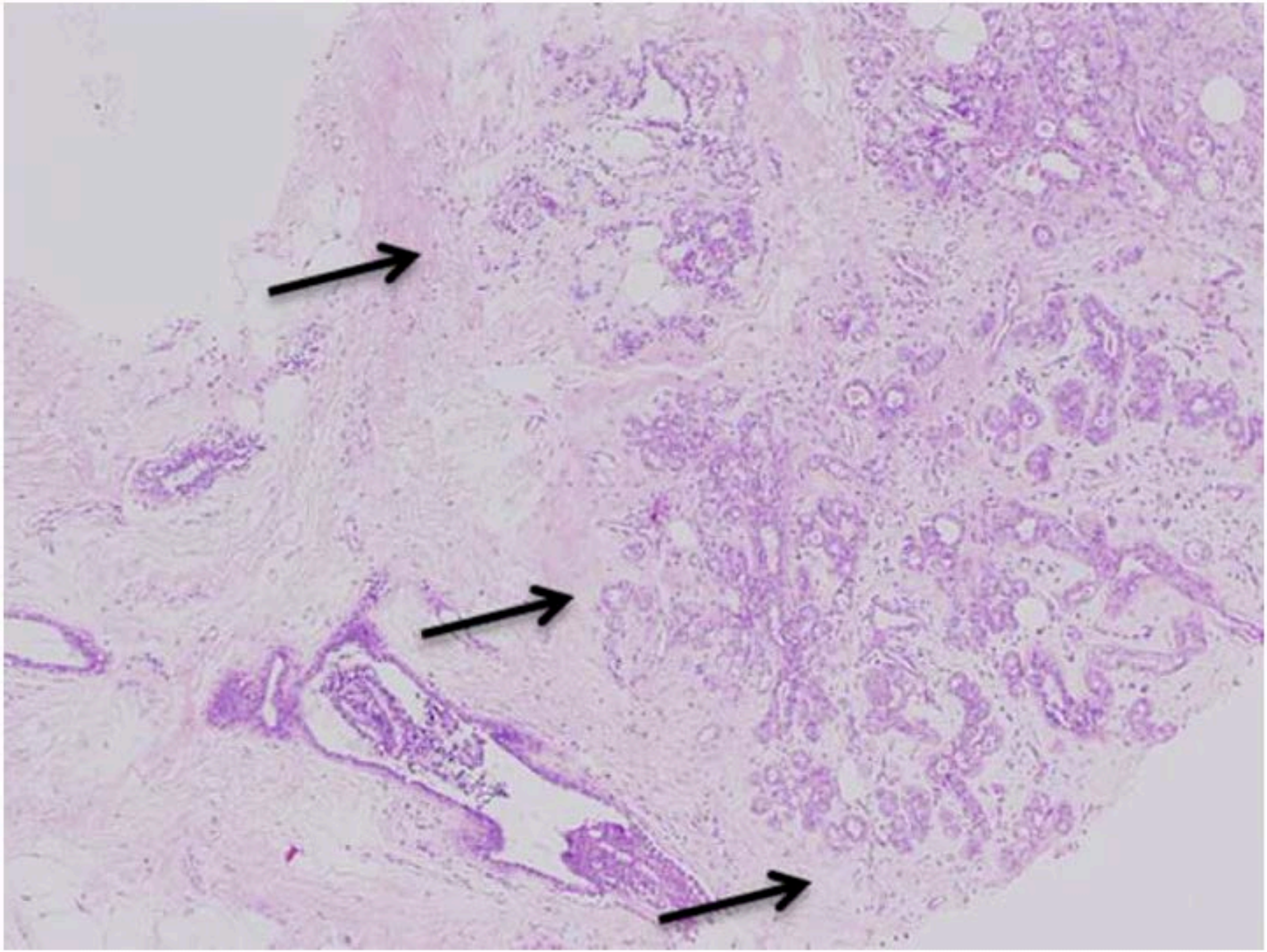

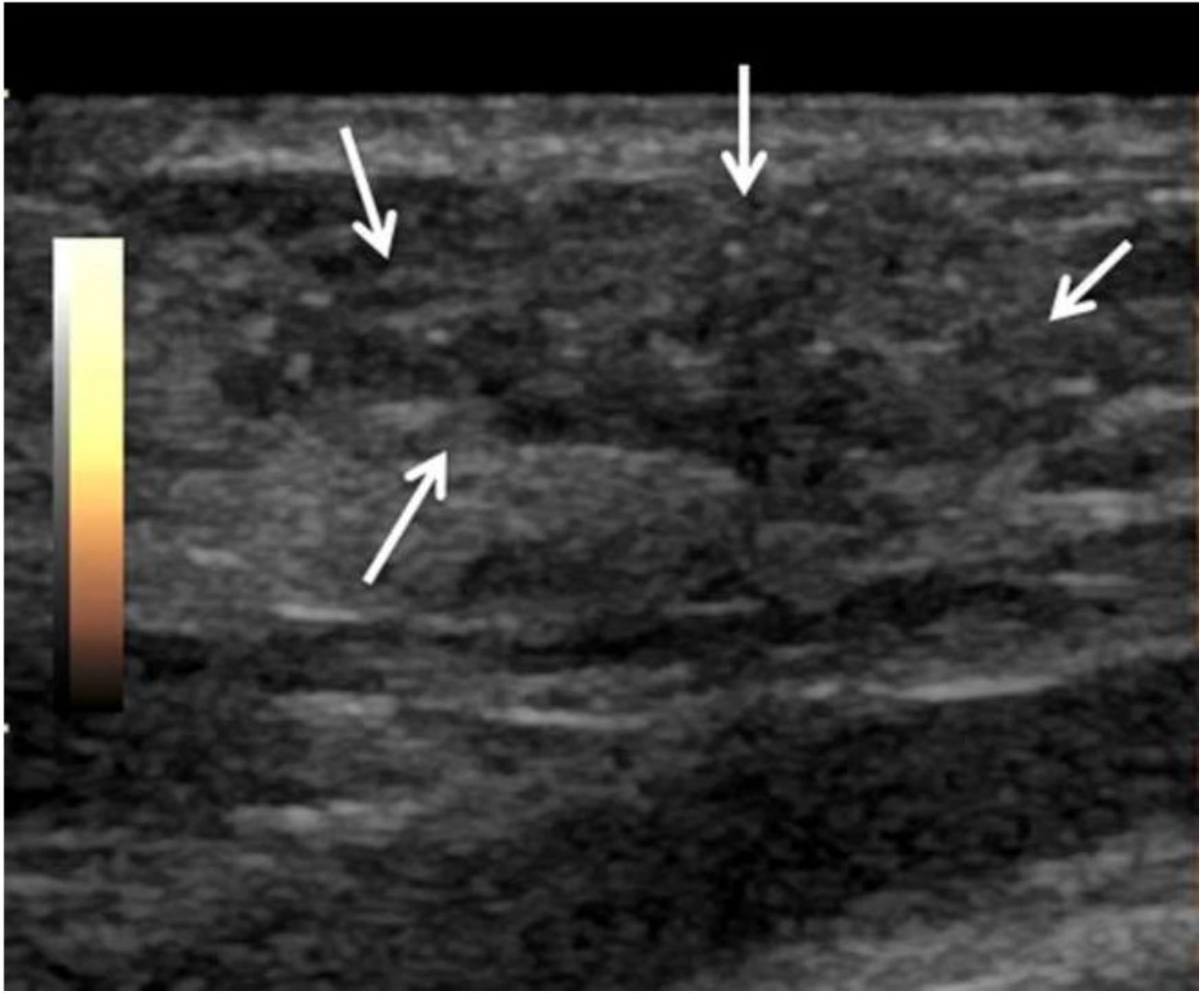

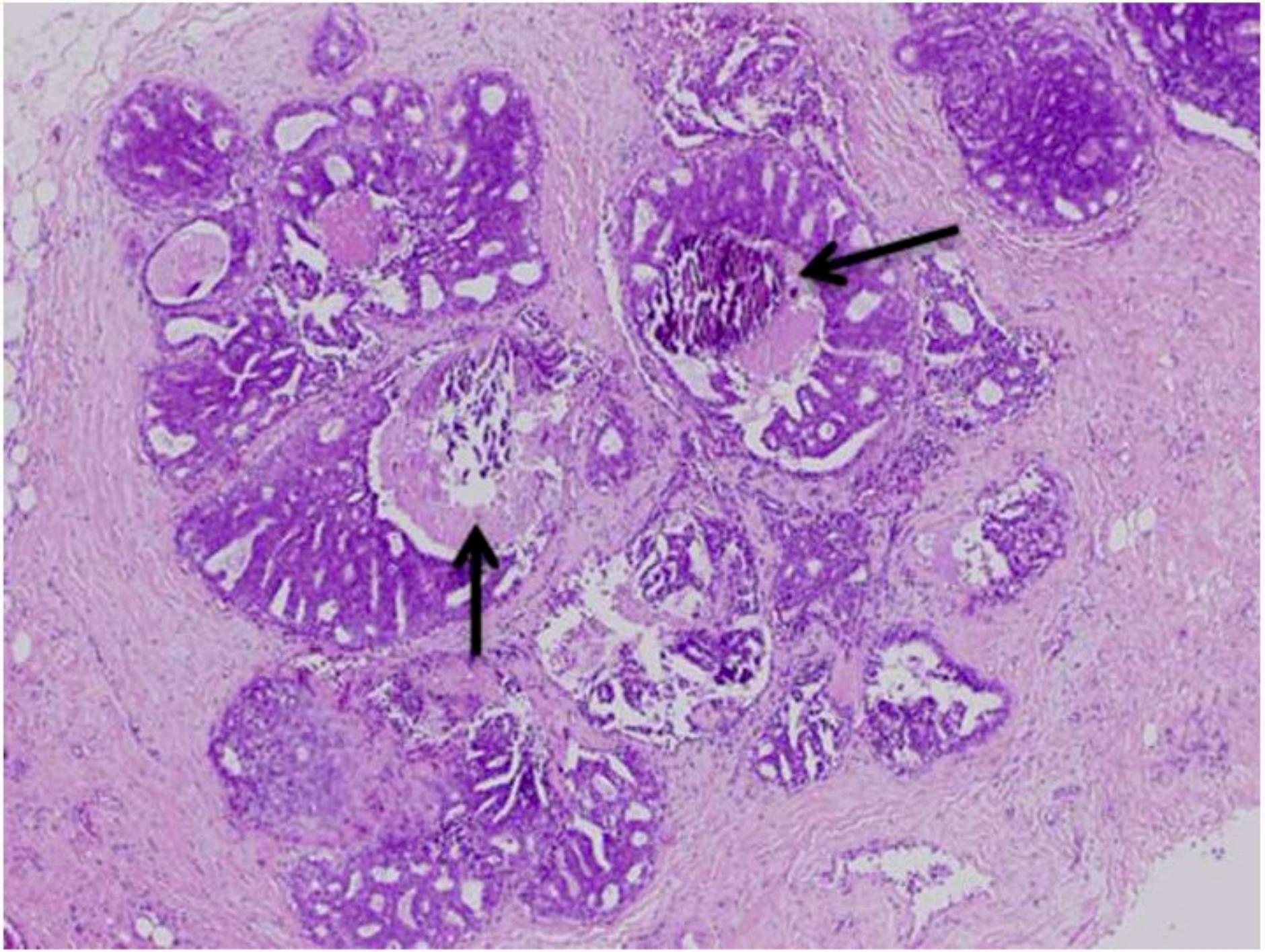

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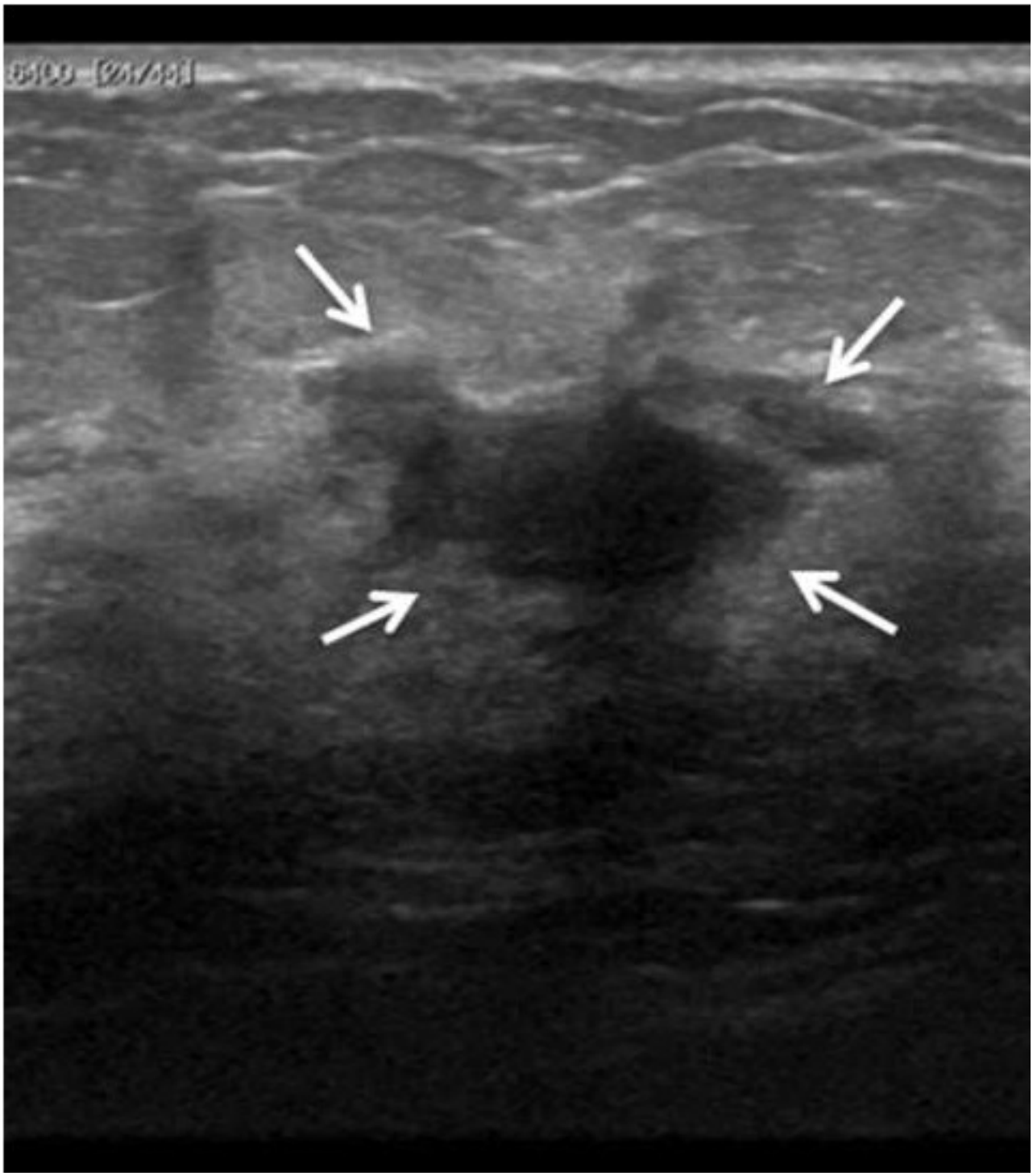

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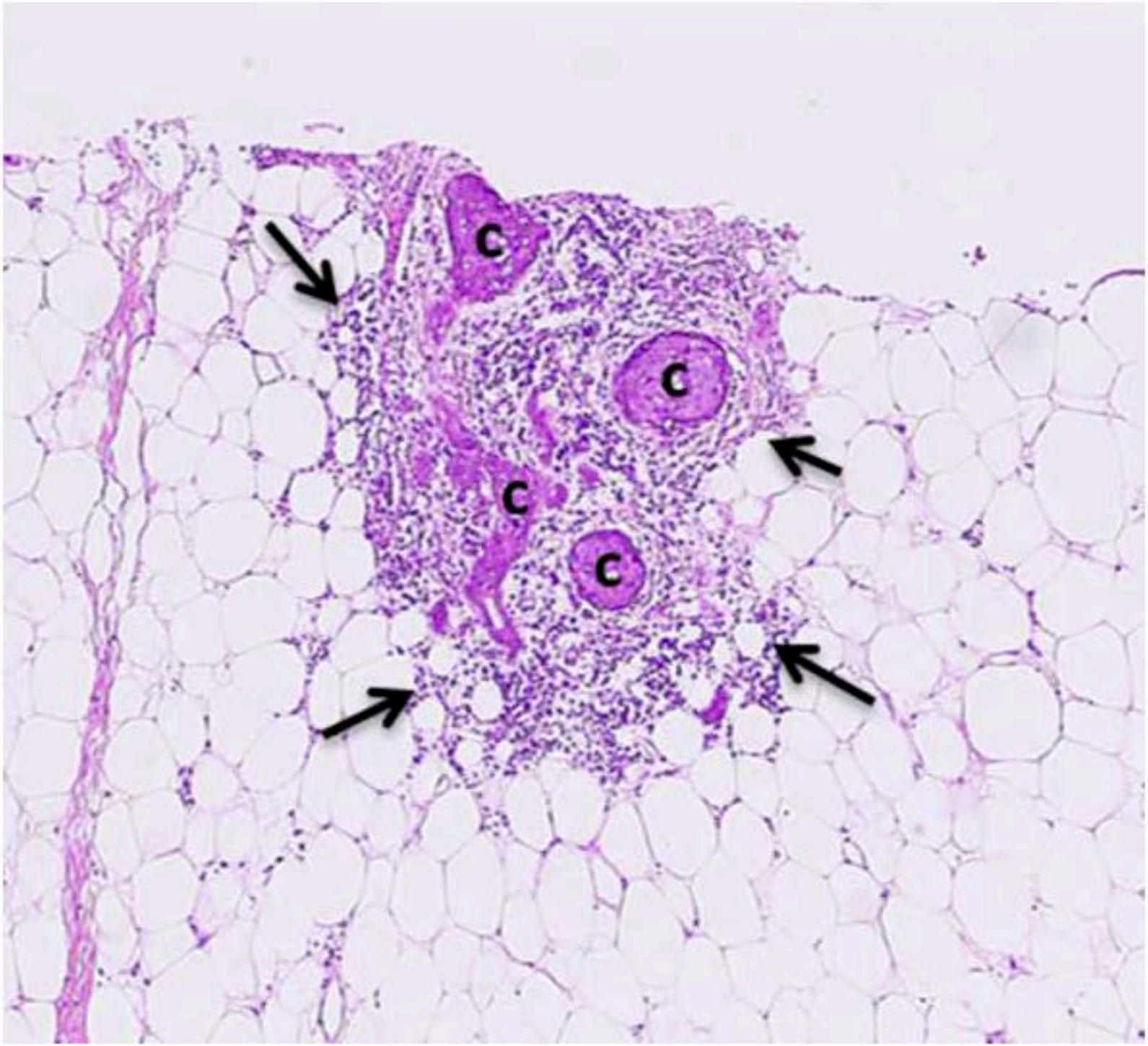

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